Appendix K.

a. Sample size

The number of patients enrolled in the study must be statistically justified. Single sample hypothesis testing formulation is a method that can be used to establish sample size. Using this method, it can be demonstrated that the complication rates associated with the investigational device are not two times as high as the OPC. The appropriate null hypothesis is one-sided: the true rate associated with the investigational device (study) is equal to or greater than 2 times the OPC. To reject this null hypothesis is to conclude that the study device is less than 2 times the OPC. Based on the Poisson distribution, (with probabilities of Type I and Type II errors of 0.05 and 0.20, respectively) the amount of data necessary to test against the smallest OPC of 1.2% per patient year (excluding valve thrombosis, and stratification for major versus minor hemorrhage, and perivalvular leak) is 800 valve years (aortic and mitral)[10].

If all patients were inducted in one year, and followed for an additional year, with an attrition rate of 5%, the total number of patients would be 556. If the patients were enrolled over a two year period, the number of patients required would be 422.

Establishing a minimum number of valve years, as apposed to a minimum number of patients, allows the manufacturer to specifically design their study to address the issues of enrollment rate, number of centers included, number of physicians implanting the device, etc. However, in order to provide a sufficient amount of data at longer follow-up times, as well as data on position specific complications, some criteria for achieving the 800 valve-years of follow-up have been established:

> There must be at least 400 valve years of follow up on each position (aortic and mitral).
>
> The clinical study must be conducted at a minimum of 3 primary centers, with 50 patients in each position (aortic and mitral) at each center. These 300 hundred patients must be followed for at least one year.
>
> Complete follow-up data must be available on a minimum of 15 patients of each size and position, and these patients must also be followed for one year.

The pooling of data from the aortic and mitral positions is justified by the fact that the data available to the FDA show that short-term morbidity rates are not a significant function of implant position (as determined by the literature review, and a review of clinical data which have been received in PMA applications). Similarly, the complication rates in each position for the study valve should not be significantly different. In order to facilitate a comparison between the rates for each position (or a comparison between the rates from each position and the OPC), there must be a sufficient number of patients implanted in each position. The sample size estimate per size is based on echo-Doppler data (effective orifice area). In order to achieve a 95% confidence interval level, the required number of implants per size is 15.

If the sponsor of the investigation desires to support any specific labeling claims, or if the study valve is available for use in only one implant position, a modified hypothesis which will be tested must be clearly established while the study is being designed. A good hypothesis is specific, simple, and formulated in advance. The use of a null hypothesis versus an alternative hypothesis should be considered. The design of the clinical study must assure that the information needed to support the claims for the device is collected. The number of patients enrolled in the study must be statistically justified. The use of a randomized, concurrent control, when appropriate, is encouraged.

Regardless of the study design, it is the responsibility of the manufacturer to ensure that the appropriate information is collected. Specifically, the manufacturer must ensure that the clinical-data collection forms used by the investigators/institutions are consistent with the protocol. Furthermore, when drafting the protocol, the manufacturer should consider that there must be consistency between the indication which is being studied, the patient inclusion criteria for the study, and the patient consent form.

b. Study population

The inclusion and exclusion criteria must be clearly established. The criteria must specify the target population (i.e., those for which the device is intended) and the accessible population (i.e., those that will be entered into the study), and any differences which may exist. It should be noted that if the target and the accessible populations are not the same, labeling restrictions may be enforced before marketing approval for the device is granted. The design must also include a plan for sampling (i.e., random, consecutive, judgmental) plus plans for recruiting subjects, considering the goal is not only to recruit an adequate number of patients, but also to minimize selection bias without compromising patient rights and welfare.

c. Predictor variables/Confounding factors

The baseline information must be collected for each patient enrolled in the study. Patients must be enrolled in the study before implantation, although in some instances it may be necessary to censor patients at a later date (due to limited size availability of stentless valves). Potential confounding factors must be considered, so that they can be controlled for when possible.

d. Outcome variables

(1) NYHA classification

The New York Heart Association (NYHA) classification must be determined for all patients. The clinical protocol must clearly establish whether functional or therapeutic classifications are to be determined.

(2) Blood data

Values of the following blood parameters must be collected on all patients: red blood count (RBC), white blood count (WBC), hematocrit, hemoglobin, serum lactate dehydrogenase (SLDH), haptoglobin, and reticulocytes.

(3) Cardiovascular complications

The application must contain a complete reporting of complications (which is currently defined as operative mortality, morbid events, and consequences of morbid events). A listing of all complications, including those not listed in the guidance document, that were experienced by the study cohort must be supplied. All episodes of each complication must be included, although a separate analysis of the complications may be prepared with the non-valve related events omitted. Adequate documentation must be supplied to support the contention that an event is non-valve related.

The morbid events included in the reporting are: angina, anticoagulant related hemorrhage, arrhythmias that require therapy, cardiac arrest, endocarditis, heart failure, hemolysis, myocardial infarction, nonstructural dysfunction, perivalvular leak, structural deterioration, thromboembolism, thrombosis (valvular). Consequences of morbid events which must be included are: explant, reoperation, and death. Definitions for these complications are provided in appendix L.

For death the cause of death must be established, and an autopsy performed when possible. An explant analysis must be conducted in all cases when a valve is explanted, and when an autopsy is conducted. You must consider including language in your investigator's agreement which indicates that it is the investigator's responsibility that these analysis must be conducted in accordance with appendix J.

The patient data forms should be designed to collect information on secondary events, although these events will not be included in the event rate calculations (see section VI.B.4.b.(3)).

(4) Hemodynamic data

The recent introduction of a non-invasive technique (echocardiography) for establishing hemodynamic performance of heart valves, has lead to the elimination of the FDA requirement for catheterization data. This change is aimed at minimizing the risk to which the patient is subjected. However, catheterization data was required on only seven patients with the largest and on seven patients with the smallest of each type (aortic and mitral) valve. However, due to the non-invasive nature of echocardiography, hemodynamic performance data must be collected on 100% of the patient population. A recommended protocol for conducting this type of study can be found in appendix M.

Catheterization data, if gathered for diagnostic purposes, can be used as supporting data in the PMA. It can not, however, be used to replace the well controlled collection of echocardiographic data on the entire patient population.

The echo-Doppler data which must be collected in order to calculate the relevant hemodynamic end points are listed in table 1 of appendix M. Pooling of data of different sizes is acceptable if the sub-structure of the valves is the same (e.g., the 29 mm and 31 mm valves are made with the same orifice, however the 31 mm has a larger sewing ring), as computer modeling was conducted by OST which showed that the effect of the constructing a 31 mm diameter tube with a 29 mm orifice will effect hemodynamic performance less than the variations associated with the measurement technique used to monitor pressure drops and effective orifice area (i.e. echo-Doppler). While pooling of this data is acceptable, it must also be presented separately for each size in the application.

e. Follow up

Telephone follow up is not acceptable, except to verify the death or loss-to-follow-up of a patient. Ideally, the patient will be seen by the investigator. The clinical data listed below must be collected at the following follow-up intervals:

<u>General information (to be collected at all follow-up periods):</u>

(i) Patient name
(ii) Patient ID number
(iii) Primary investigator
(iv) Institution
(v) Date

Pre-operative demographic information:

(i) Patient age or date of birth
(ii) Patient sex

Pre-operative clinical data:

(i) Valvular lesion (e.g. stenosis, regurgitation, valve dysfunction)
(ii) Etiology (e.g., congenital, rheumatic, mitral valve prolapse, calcification, structural deterioration, bacterial endocarditis, trauma, failed repair, papillary muscle, dysfunction, chordae tendineae rupture, etc.)
(iii) Cardiac rhythm (e.g. sinus, atrial fibrillation, flutter, paced, heart block)
(iv) NYHA classification, as described above
(v) Coexisting cardiovascular conditions (e.g. congestive heart failure, atrial enlargement, cardiomyopathy, coronary artery disease, previous myocardial infarction)
(vi) Previous cardiovascular operations (e.g. coronary artery bypass, percutaneous valvuloplasty (position), operative valvuloplasty (position), annuloplasty (position), previous replacement)
(vii) Other coexisting medical conditions (e.g. liver, kidney, and lung disease, history of alcohol or drug use, diabetes, hypertension, history of endocarditis)
(viii) Blood studies, as described above.
(ix) Pre-operative catheterization and/or echocardiography data, if collected. See appendix M.

Operative data:

(i) Date of implant
(ii) Valve serial number
(iii) Valve model number
(iv) Valve tissue annulus diameter
(v) Condition of valve being replaced
(vi) Condition of annulus/debridement procedures
(vii) Surgical procedure
(viii) Suture technique (e.g. continuous or interrupted)
(ix) Concomitant procedures (e.g. pacemaker implant, coronary artery bypass)
(x) Intraoperative complications (e.g. hemorrhage, sizing problems, difficulty weaning from bypass), including those described above.
(xi) Intraoperative catheterization data and/or echocardiography data, if collected. See appendix M.

Early Post-operative (30 days) /Discharge data:
(whichever comes last)

(i) Cardiac rhythm
(ii) Anticoagulation therapy (e.g., warfarin, heparin, dipyridamole, aspirin or other platelet inhibitor)
(iii) Coagulation profile (including prothrombin time and partial thromboplastin time, and international normalized ratio (INR)), as appropriate
(iv) Cardiovascular complications, including, but not limited to those described above
(v) Echocardiography study for all patients. See appendix M.
(vi) Catheterization data, if collected.

Late Post-operative data (3 - 6 months):

(i) Length of time since implant or implant date
(ii) Type of visit (i.e., office, hospital, or referring physician)
(iii) Cardiac rhythm
(iv) NYHA classification, as described above
(v) Blood studies, as described above
(vi) Anticoagulation therapy
(vii) Coagulation profile (including prothrombin time and partial thromboplastin time, and international normalized ratio (INR)), as appropriate
(viii) Cardiovascular complications, **as described above**
(ix) Catheterization and/or echocardiography data, if collected. See appendix M.

Annual follow-up (11-14 month, **and yearly after**):

(i) Length of time since implant or implant date
(ii) Type of visit (i.e., office, hospital, or referring physician)
(iii) Cardiac rhythm
(iv) NYHA classification, as described above
(v) Blood studies, as described above
(vi) Anticoagulation therapy
(vii) Coagulation profile (including prothrombin time and partial thromboplastin time, and international normalized ratio (INR)), as appropriate
(viii) Cardiovascular complications, as described above
(ix) Echocardiography study for all patients. See appendix M. **(required at 11-14 month follow up only)**
(x) Catheterization data, if collected.

4. Data Analysis

The establishment of safety and efficacy of a replacement heart valve must be based on, at a minimum: an analysis of changes in NYHA classification, occurrences of cardiovascular complications, blood data, and hemodynamic data. Data for single and double valve replacements must be analyzed separately.

a. Pooling of data

Due to the fact that the primary centers are utilizing a common protocol, it may be possible to pool the data, and analyze it collectively. This is desirable, as it reduces the number of patients necessary to support an indication for use. However, the use of a common protocol at the primary centers, in and of itself, is not sufficient to justify the pooling of the data. A discussion which shows that the PMA cohort is representative of the patient population for which the device is intended must be provided. In addition, it must be shown using an appropriate statistical analysis (e.g., a chi-squared test) that the population of each center is similar, and therefore, generally representative of the target population. Furthermore, if foreign data is used, in addition to the information required to allow for the use of this type of data, a statistical analysis must be used to establish that the foreign cohort is comparable to the U.S. PMA cohort.

The comparisons must be based on, at a minimum, the following demographic and pre-operative variables: age, sex, etiology, previous heart valve replacement surgery, valvular lesion, and pre-operative NYHA, concomitant cardiac procedures (e.g. coronary artery bypass), and coexisting cardiovascular conditions. Also, included in the analysis must be the position of implant, size of implant, and anticoagulation therapy. Furthermore, even though identical protocols are used, and demographic variables are comparable, center to center variations in clinical results may exist. Therefore, establishing the poolability of data must take into account outcome variables as well. At a minimum, the following outcome variables must be considered: complication rates (1 year actuarial) for thromboembolism, thrombosis, anticoagulation related hemorrhage, explant, and death; and improvement in NYHA classification. Any differences which are found between centers must be discussed in terms of overall expected variations in valve-recipient populations, and clinical results following valve implant.

b. Outcome variables

(1) NYHA classification

NYHA classification data must be analyzed to demonstrate if the implanting of the study valve leads to an improvement in this clinical parameter. Data must be presented for the entire populations, and must also be stratified by implant position, and valve size.

(2) Blood data

Blood data must be analyzed to determine if significant subclinical and unreported hemolysis is occurring. A discussion of the changes in blood variables with time must be provided. For example, an elevation of serum lactate dehydrogenase (SLDH) is expected in the early post-operative period with a valvular replacement. The relevant question is whether this will lead to anemia in the late post-operative period. Therefore, the analysis of the blood data must include a trend analysis for two post-operative data points (3 to 6 months, and 11 to 14 months), to determine if hemolysis is increasing with time. The following parameters must be included in this trend analysis: SLDH, hemoglobin, hematocrit, and reticulocyte. In addition, include a discussion of the patients' ability to compensate for any abnormalities in blood variables which are present. Specifically, does an overall analyses of all the blood parameters indicate that stable intravascular hemolysis is occurring, as opposed to uncompensated anemia.

For the blood parameters which are measured, the results of the patients in the study must be compared to the expected values for the entire population. The mean value of a blood parameter is a often a poor indicator of normality, since it is possible to have several, or even all, of the individual results outside the normal range and still have the mean within the normal range. Therefore comparisons must be made against normal ranges of the parameters, not a single mean value. Data could be reported as the percent of patients for whom the individual results are within the normal ranges. Furthermore, for specific parameters, center-to-center variations are quite large. For these parameters, the results for the individual patients must be normalized to center ranges, not to overall population ranges. The parameters for which center normal ranges must be considered include, at a minimum, serum LDH and haptoglobin. SLDH must be normalized as a percentage of the upper range of normal for each center, and if elevated, fractioned by source.

This analysis must also explicitly establish the criteria used to establish the presence of clinically significant hemolysis.

Data must be presented for the entire population, and must also be stratified by implant position, and valve size.

(3) Cardiovascular complications

The following measures of (disease) frequency must be calculated for all complications:

(i) for the early post-operative period (before 30 days or discharge, whichever comes first), rates must be calculated as a percent of patients who experience the complication.

(ii) for the late post-operative period, an estimate of average rates must be calculated. The linearized rates must be reported as the number of events per 100 years of patient exposure. The calculation of a linear rate assumes that the hazard function of an event is constant with time. However, for most of the complications under consideration, the early post-operative rate is significantly higher than the late post-operative rate. Therefore, complications which occur in the early post-operative period must not be included in the calculation of linearized rates.
(iii)An estimation of risk must be completed for all of the reported complications (early and late). An actuarial analysis must be used to construct life tables to show estimated probability of freedom from the complication at the end of each time interval for time to first occurrence of each complication. Follow-up for complications must include evaluation based on quarter-years post implant[11,12].

Secondary morbid events should not be included in the calculations of complication rates. However, <u>each consequence of a morbid event (explant, reoperation, death) must be included in the calculation of complication rates</u>. For example, if a patient has endocarditis, which produces a perivalvular leak, and subsequently the valve is explanted, it is not necessary to include perivalvular leak in the complication rates. However, information on secondary complications should be collected on the patient data forms, as it allows for the complete and appropriate tracking of the course of events associated with each individual patient. Data forms should be designed to identify secondary complications as such, and should facilitate data-form audits.

For the statistical analysis of complication rates, the discussion must include a description of how and why patients were censored from the study. For patients from which the study valve is explanted, can the patient be re-entered into the study if a new study valve is implanted? Also, the methodology for handling multiple-occurrences of the same event must be discussed.

In addition, demonstrate that the observed rates for the study valve are significantly less than 2 times the OPC, as outlined in section VI.B.3. Since complication rates do not differ by position, data from the two positions may be combined for the purpose of the OPC test. However, in order to justify this pooling for the study valve, it must be shown that there is no significant difference between the position. The methodology of showing comparability between positions is left to the discretion of the manufacturer.

You must specifically analyze the data to determine any effect of valve tissue annulus diameter on complication rates, although the data will most likely not be statistically significant. Where appropriate, the complications must be stratified as valve related versus non-valve related.

In addition to the general requirements, specific complications must be stratified as follows:
For thromboembolism must be stratified by anticoagulation therapy and concomitant cardiac problems (atrial fibrillation, sinus rhythm, pacemakers, etc.);
Nonstructural deterioration and structural dysfunction must be stratified by the nature of the dysfunction (e.g. pannus formation, calcification, perforation, tearing, stent failure, leaflet failure, orifice failure, orifice impingement, etc.);
Reoperation and explant must be stratified by fatal versus non-fatal events.

(4) Hemodynamic performance

Calculations of the echocardiographic data must conform to tables 2 and 3 of appendix M, and must be summarized as illustrated in tables 4 and 5 of the same appendix. If catheterization data are included in the PMA, the following parameters must be calculated: mean mitral valve gradient, peak systolic and mean aortic gradient, mitral valve area or index, aortic valve area or index, cardiac output. Also, an angiographic assessment of regurgitation, if conducted, must be included.

c. Confounding factors

Hazard regression analysis must be applied to identify risk factors (gender, age at implant, pre-operative NYHA classification, previous valve surgery, concomitant coronary artery bypass surgery, implant position, implant size) which might affect the incidence of reoperation, explant, and death.

d. Follow up rates

For <u>each</u> follow up period at which a specific variable is collected, and <u>each</u> parameter (NYHA classification, blood data, reports of complications, echo-Doppler) analyzed, a table must be constructed which shows the number of patients eligible for follow up at the cut off date, the number of patients for which follow up data are available, and the percent follow up.

e. Additional Information

The following additional information must also be included:
list of complications by patient identification number;
summary of early deaths;
summary of late deaths;
summary of patients not completing study (due to lost-to-follow up, death, or explant);
summary of patient complaints received;

all patient data forms for a 10% random sampling of the patient population;
copies of patient data forms for all patients not completing the study;
explant analysis must be conducted in all cases when a valve is explanted or an autopsy is performed;
death reports must include autopsy reports, when available, especially when the cause of death has been classified as non-valve related;
a summary of the data auditing procedures.

VII. One Investigator

If only one clinical investigator was used, give a justification showing why this is sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of test results.

VIII.Reports and Other Information

A. Bibliography

A bibliography of all published reports not submitted under CFR 21 814.20(b)(6), whether adverse or supportive, that concern the safety and effectiveness of the device must be included.

B. Other data

Identification, discussion and analysis of any other data, information or report (foreign or domestic) relevant to an evaluation of the safety and effectiveness of the device must also be included.

C. Panel requests

Copies of any published reports or unpublished information; if FDA or an FDA advisory committee requests.

IX. Samples

Only if requested.

X. Labeling

Must be included in manufacturing section.

XI. Environmental Assessment

If claiming a categorical exclusion, information to justify the exclusion, or an environmental assessment.

Post approval requirements

The annual (postapproval) report required under 21 CFR 814.84, and in the "Conditions of Approval" must contain all reports of complications from any source, foreign or domestic, including information derived from commercial marketing experience, clinical surveillance and epidemiologic studies, reports in scientific literature, and unpublished scientific papers. In addition, it must contain the data obtained from the postapproval study. This postapproval study is separate and distinct from the postmarket surveillance study required under section 522(a)(1)(A) of the act, although it may be possible to justify the use of a common protocol to conduct both studies. The postapproval study, which is reviewed by ODE, must be designed to evaluate the long-term safety, efficacy, and durability of the valve. The postapproval study protocol that outlines the design of the study, collection of follow-up data, analysis of the data, and format for reporting the results in the annual (postapproval) report must be submitted prior to PMA approval. The proposal must, at a minimum, address the following:

(i) a sample size estimate with supporting rationale;

(ii) a specific set of study objectives with realistic safety and efficacy endpoints, and

(iii) in order to quantify complication rates, an estimate of the numerator and denominator must be established.

To assist in preparing these reports, the manufacturer can consult the "Guidance for the Preparation of the Annual Report to the PMA Approved Heart Valve Prosthesis." As noted in the "Conditions of Approval", the annual report, containing the results of the annual (postapproval) study is due on the anniversary date of the original approval of the PMA.

Supplements to the approved PMA

Supplements to an approved PMA must be submitted in accordance with 21 CFR 814.39. Modifications to the device may require collecting <u>in vitro</u> and clinical data to establish that the modification has not adversely effected the safety and effectiveness of the device. Requirements have been established for specific design modifications.

<u>Modifications to the Sewing Ring Configuration</u>

Clinical data is not required to establish the safety and effectiveness of alternate sewing ring configurations. Panel consideration of this issue indicated that changes in sewing ring configuration will not alter hemodynamic performance of the device, as the sub-structures of the valve have not been altered.

The clinicians who provided input into this subject indicated that clinical data would not be necessary to validate changes in sewing ring diameter of less than 15%, as long as the overall diameter of the orifice has not been changed (e.g, if the additional material is being added to the sewing ring, the additional material should not be interfere with flow). Additional computer modeling was conducted by OST which showed that effect of the sewing ring in hemodynamic performance will be less than the measurements technique used to monitor pressure drops and effective orifice area (i.e. echo-Doppler). Data which would be required to validate this change include, at a minimum, in vitro studies which clearly establish that the new sewing ring can support the physiological loading.

Modifications to the Sewing Ring Material

Clinical data has been collected which shows that polytetrafluoroethylene (PTFE) and polyethylene terephthalate (PET) are materials from which clinically acceptable replacement heart valve sewing rings can be fabricated. Therefore, the validation of the use of these materials can be achieved with animal data which examines the healing characteristics of the sewing ring, if the animal data is supplemented with explant data. The application for this type of change must also discuss the comparability of the specific material (manufacturer, weave, etc.) with those currently used in valves approved for marketing clearance. The use of alternate sewing ring materials other than PTFE and PET would require clinical data.

Valved Conduits

Generally, marketing clearance for valved conduits can be obtained without collecting additional data if both the valve and the graft have previously been cleared for marketing. The validation of the design must include, at a minimum, in vitro studies which clearly establishes that the valve/graft interface can withstand physiological loading. If a coated graft is used, in vitro studies could be conducted to determine if the manufacturing steps associated with the sewing of the valve into the graft have adversely effected the coating, and subsequently the bleeding at implant.

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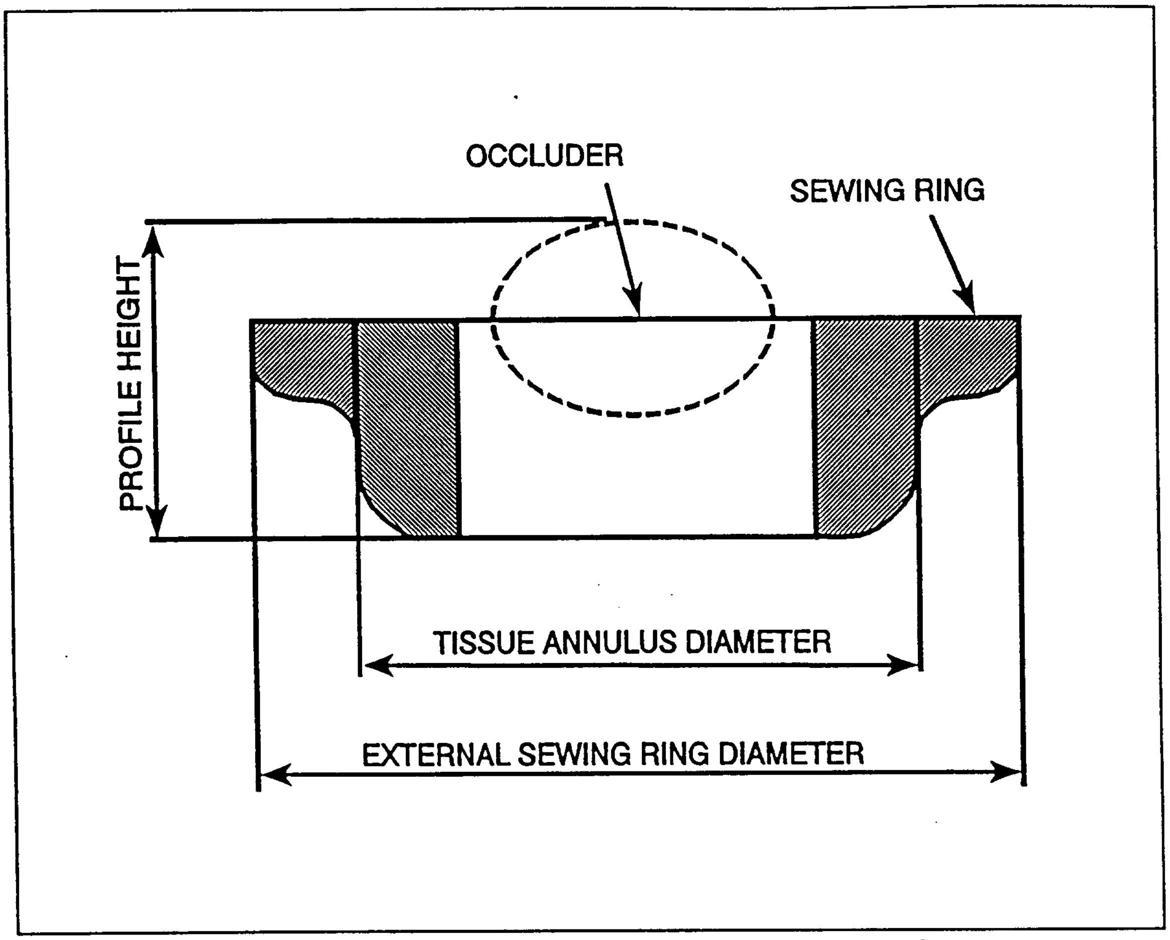

Figure 1 Designation of Dimensions of Replacement Heart Valves.

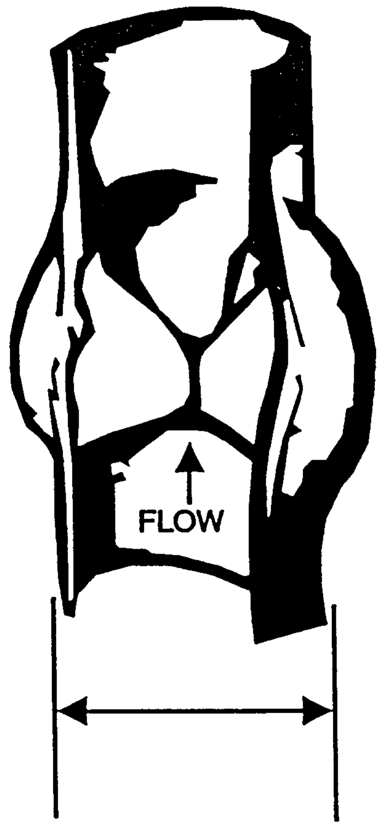

Figure 2 Designation of Dimensions of Replacement Stentless Heart Valve.

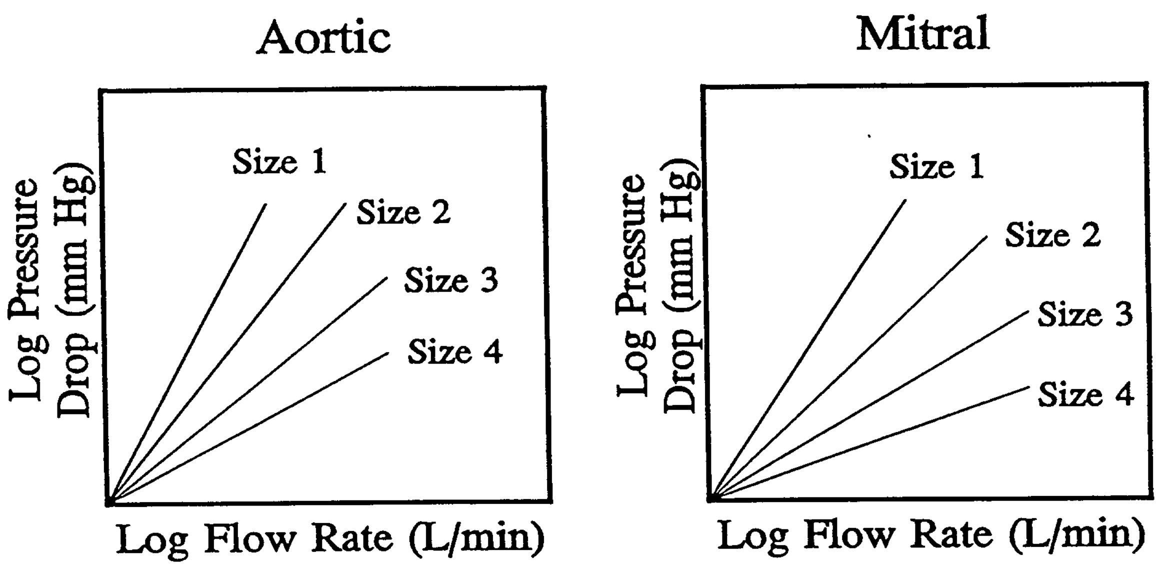

Figure 3
Steady Flow Pressure Drop Data

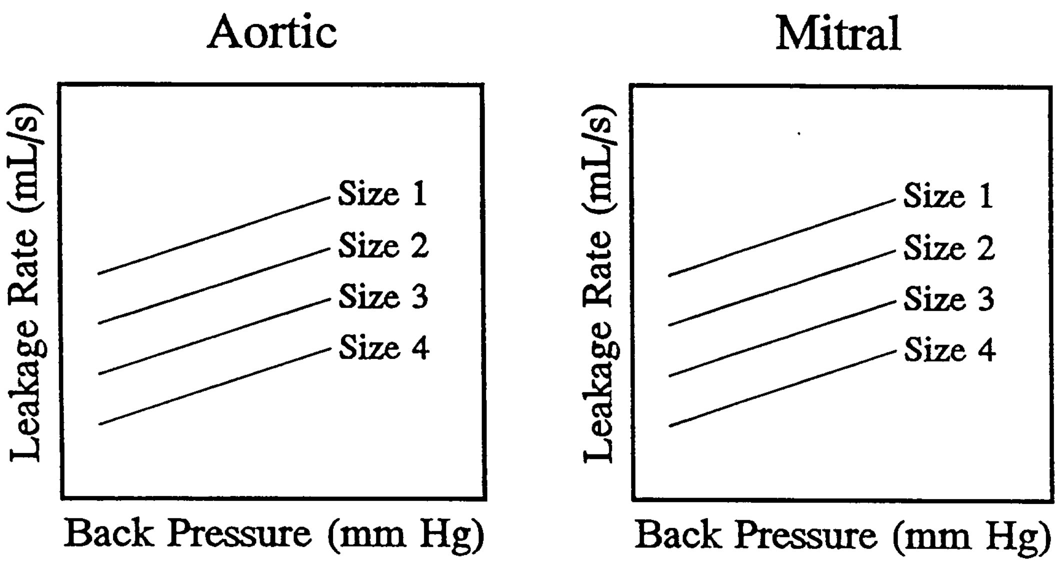

Figure 4
Back Pressure Leakage Data

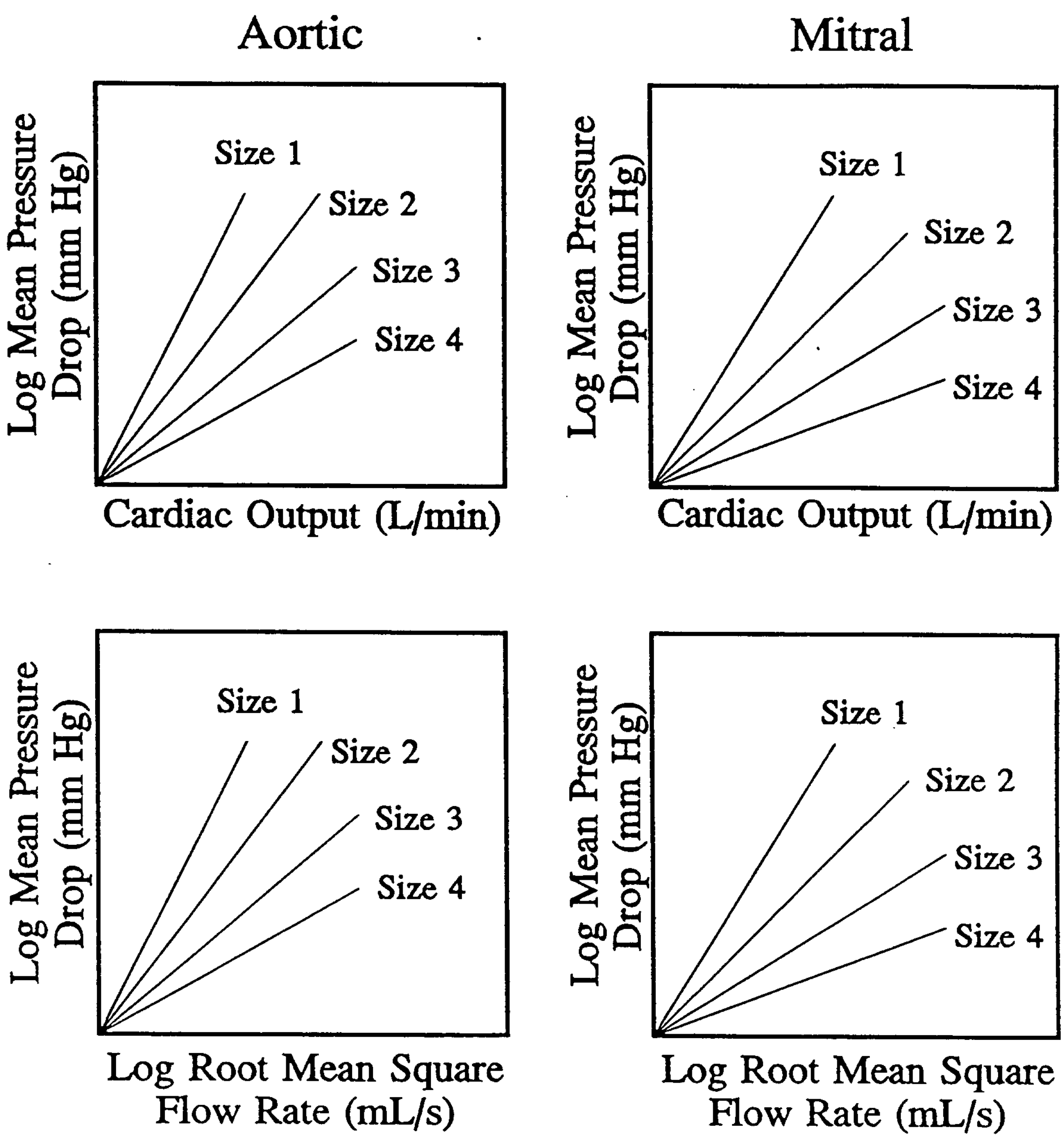

Figure 5.
Pulsatile Flow Pressure Drop Data

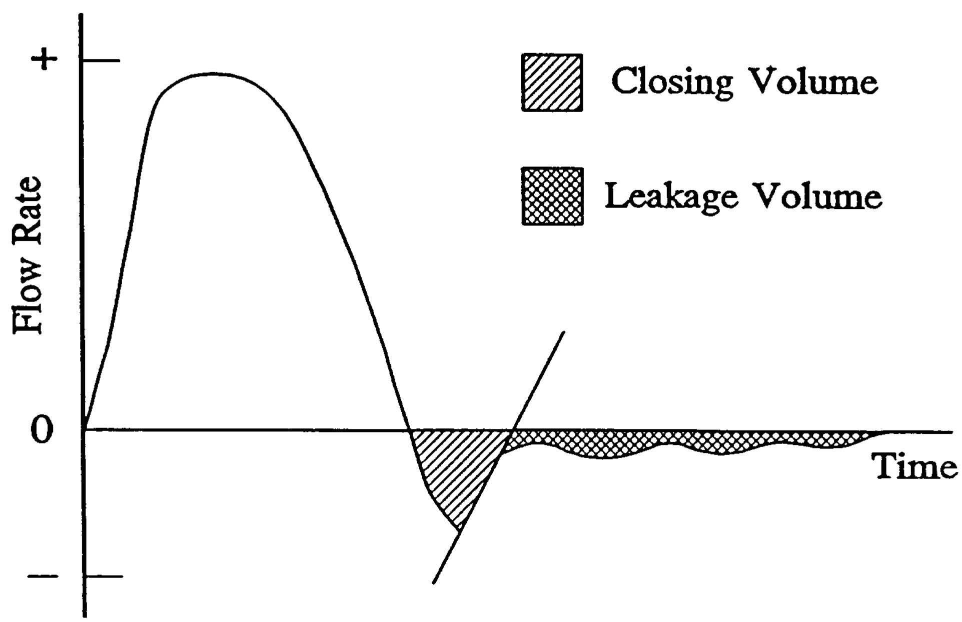

Figure 6
Regurgitant Volumes

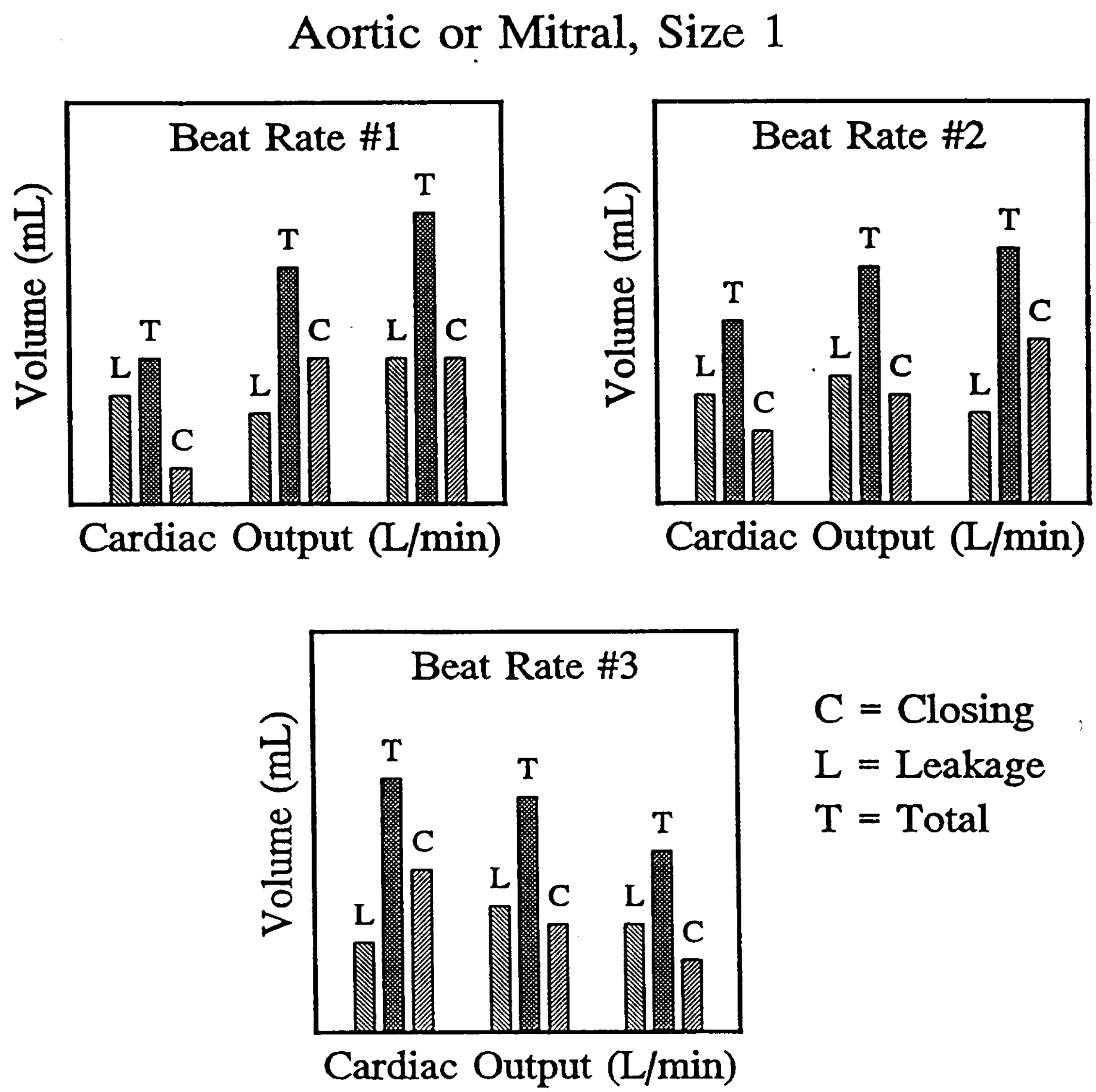

Figure 7
Dynamic Regurgitation Data